REMARKS

Applicant filed a request for continued examination (an RCE) for the present patent application after an appeal was filed (to the Board of Patent Appeals) but before a decision on the appeal. The appeal has been withdrawn and prosecution has been reopened.

Claims 1-20 are pending in the present patent application. Claims 1-20 have rejected.

Claims 1-20 have been rejected under 35 U.S.C. 103(a) over PCT application WO 90/15070 to Pirrung et al. (hereafter referred to as Pirrung) in view of U.S. Patent 4,436,826 to Wang et al. and U.S. Patent 6,041,095 to Yokhin (hereafter referred to as Yokhin).

Pirrung teaches a method for determining chemical binding using binders and photo-activated receptor arrays. According to Pirrung, an array is activated for binding using radiation. The radiation exposure results in detachment of certain chemical groups from members of the array. The activated array is then exposed to binders, and then analyzed to determine whether or not any of the binders are bound to any of the members of the activated array. According to Pirrung, this analysis is performed using autoradiographic techniques (when the binder is radioactive, i.e. is tagged with an isotope detectable through radioactive decay of the isotope), or ultraviolet/visible light techniques when the binder has a chemical tag that is observable using these other techniques. Thus, Pirrung teaches:

1) forming an array of receptors,
2) irradiating the array to activate it for binding, and thereafter,
3) exposing the array of activated receptors to binder(s), and
4) analyzing the array to see if chemical binding has occurred between any of the activated receptors and binder(s).

According to Pirrung, the activation step must occur before binding can occur. Pirrung discloses several ways to analyze whether or not this binding has occurred. These ways include using autoradiography, ultraviolet light, and visible light. According to the present Office Action, Pirrung is silent with respect to using x-ray fluorescence to analyze members of an array for chemical binding.

The Wang patent, entitled "Tagged Immunoassay" (hereafter referred to as Wang), is concerned with an immunoassay method for measuring the content of a target antigen or antibody in a fluid or tissue specimen. Wang teaches reacting a target antibody (or antigen) with a reagent antibody (or antigen) that forms a complex with the target antibody (or antigen). Wang also teaches that the reagent antibody (or antigen) is tagged with tagging elements (latex particles with metal particles embedded in the latex particles). Wang refers to these tagged materials as mobile units. According to Wang, the tagging elements are unassociated chemically with the reagent antibody or antigen, and also are protected against reacting with the target and with the biological and chemical environment of the assay. A complex that forms between a target antigen and a tagged reagent antibody is detected by measuring the radioactive decay or x-ray fluorescence of the tagging element. Wang does not teach or suggest irradiative activation of any material, or of forming arrays of materials (such as the antibodies or antigens that are disclosed in Wang). Wang also does not teach or suggest any method that does not involve tags.

Yokhin teaches an apparatus for performing x-ray fluorescence, but does not teach or suggest a method for detecting chemical binding, or using x-ray fluorescence to detect chemical binding, or using x-ray fluorescence to detect chemical binding of chemicals to members of an array. Applicant had argued previously that Applicant's claimed invention was not obvious over Pirrung in view of Yokhin. According to the according to the present Office Action, Applicant's previous argument about the improper combination of Pirrung and Yokhin "...is moot in view of the newly applied reference of Chia-Gee Wang who teaches X-ray fluorescence in detecting binders (i.e. antigen and antibody)...", so it is not clear how or why Yokhin is being applied again to reject Applicant's claims in the present Office Action.

According to the present Office Action, it would have been obvious to one of ordinary skill in the art to select or include x-ray fluorescence in the detection method of Pirrung, as taught by Wang, because different target antigens or antibodies can be assayed simultaneously by employing different tagged mobile units and the mobile units with the tagging elements can be recovered for disposal or reuse.

Applicant's claimed method involves:

1) forming an array of receptors,
2) exposing the array to binder(s),
3) irradiating the array with X-rays to induce an x-ray fluorescence signal after the receptors are exposed to binders; and
4) detecting x-ray fluorescence from at least the binder and analyzing the x-ray fluorescence to see if chemical binding has occurred between any of the receptors and binder(s).

Steps 1 and 2 can be reversed, so the receptors can be exposed to binders before forming the array. Claim 1 has been amended in this response. Applicant has amended claim 1 by clarifying that that the x-ray fluorescence that is detected comes from at least the binder. Applicant has described in detail in the present application that the detected x-ray fluorescence can come from just the binder if the x-ray fluorescence comes from an element present in only the binder, or from both the receptor and the binder if the detected x-ray fluorescence comes from an element that is common to both the binder and receptor.

With regard to the rejection of Applicant's claims, Applicant submits that claims 1-20 are not obvious over Pirrung in view of Wang and/or Yokhin for the following reasons. With regard to the teaching of x-ray fluorescence by Yokhin and Wang as it is being applied to Applicant's claims, Yokhin is silent about using x-ray fluorescence to detect chemical binding, and Yokhin does not teach or suggest using x-ray fluorescence with arrays of materials. Applicant has amended claim 11 by limiting the binders of claim 11 to untagged binders. No new matter has been added by this change

because the present specification discloses that Applicant's method is especially useful because tags are not required. Wang does not teach or suggest the detection of x-ray fluorescence from an array. Wang also does not teach or suggest the detection of x-ray fluorescence directly from a binder. Wang detects chemical binding indirectly by detecting x-ray fluorescence a tag that is supposed to be associated with binders (i.e. the "reagents" of Wang). According to Wang (see abstract, specification, and independent claims 1, 10, and 24), the tag is "...chemically unassociated with said reagent and are chemically protected against reaction with said target and the biological and chemical environment of said assay...". In other words, Wang's tag and Wang's binder are separate entities. Furthermore, Wang does not provide any motivation or suggestion to for adapting the method of Pirrung to detect chemical binding using x-ray fluorescence. For these reasons, Applicant submits that claims 1 and 11, as amended, are not obvious over Pirrung in view of Wang and Yokhin. Claims 2-10 are dependent from claim 1, and claims 12-20 are dependent from claim 11. These claims have all of the limitation of the parent independent claims. Applicant submits that these claims are also not obvious over Pirrung in view of Wang and Yokhin. Applicant respectfully requests that the rejection of claims 1-20 under 35 U.S.C. 103(a) over Pirrung in view of Wang and Yokhin be withdrawn.

The present Office Action includes a section entitled "Response to Arguments". In this section, the Office Action is attempting to explain the reasons why Applicant was not successful in overcoming the previous rejections of the claims under 35 U.S.C. 103(a) over the combination of Pirrung and Yokhin. There are four parts to this section. The first part deals with the absence of any teaching of x-ray fluorescence by Pirrung. According to this Office Action, Pirrung is silent with regard to x-ray fluorescence. The second part deals with the motivation to combine Pirrung with Yokhin. Applicant still disagrees with any interpretation that Yokhin provides any motivation or suggestion for combining Pirrung with Yokhin. Applicant submits that Yokhin does not suggest or provide motivation for combining the teachings of Pirrung with those of Yokhin because Yokhin does not even suggest using x-ray fluorescence to detect chemical binding. The mere mentioning by Yokhin that x-ray fluorescence is a well-known technique for determining elemental compositions does not rise to the level of a suggestion or

motivation to combine Yokhin with Pirrung to use x-ray fluorescence for detecting chemical binding between binders and members of a receptor array. The present Office Action also states that the motivation does not have to come from the cited references, but from the knowledge generally available to one or ordinary skill in the art, and that X-ray fluorescence is known in the art for evaluation of compositions. In this regard, without wishing to cite specific case law, Applicant wishes to note that there exists a substantial body of case law concerned with proper and improper combinations of references. The gist of the conclusions reached in this body of case law is that rejections based on combinations of references are improper and should be withdrawn when there is no motivation or suggestion in the references themselves for the combination. In addition, while X-ray fluorescence has been used for evaluating compositions, Applicant's claimed method involves forming an array of materials, exposing members of the array to other materials, and afterward analyzing the array using x-ray fluorescence to determine whether any of the array materials have become chemically bound to any of the other materials. Yokhin does not teach or suggest using x-rays for chemical binding. In fact, the present Office Action is now stating that "...Yokhin does not teach X-ray detection of binders...". This admission has not appeared in any previous Office Action.

The third part of the "Response to Arguments" section deals with the subject of labels or tags. According to this part, Applicant's previous argument about Pirrung requiring labels and Applicant not requiring labels was not found persuasive because this limitation was not found in the claimed invention. Applicant disagrees because claim 11 did include a limitation where the binders were not labeled with optically fluorescent tags. Claim 11 as amended in the present response recites untagged binders. Claim 11 has also been amended to clarify that it is the detecting step that indicates that a binding event has occurred or not. It should be noted that claim 1 as amended herein still includes the use of both untagged binders and tagged binders, but for a method involving forming an array, exposing the array to binders capable of being detected by x-ray fluorescence, and afterward exposing the array to x-ray radiation to induce x-ray fluorescence, and then detecting x-ray fluorescence at least from the binder.

The fourth part of the "Response to Arguments" section of the Office Action begins with "...Applicant argues that the reference does not teach how X-ray fluorescence would be combined with the teachings of Pirrung..." and continues with "...this argument has been fully considered but is moot in view of the newly applied reference of Wang that teaches detection of antigen and antibody binding using X-ray fluorescence set forth above...". With regard to Wang, Applicant has explained that Wang does not teach or suggest using x-ray fluorescence in combination with arrays, nor does Wang teach or suggest x-ray detection of a binder. Instead, Wang releases tags that are believed to become associated with a binder, and Wang detects the x-ray fluorescence from the tag. By contrast, Applicant teaches and claims detection of x-ray fluorescence from the binder.

Applicant is submitting other evidence in further support of non-obviousness.

Applicant is providing the following two review articles: (1) Zhu et al., entitled "Protein Chip Technology," Current Opinion in Chemical Biology, vol. 7, issue 1, pp. 55-63, February 2003 (hereafter referred to as Zhu); and (2) Predki, entitled "Functional Protein Microarrays: Ripe for Discovery, Current Opinions in Chemical Biology, vol. 8, issue 1, February 2004 (hereafter referred to as Predki). These review articles are concerned with microarray technology for large-scale high-throughput biology. According to Zhu, microarray technology allows for fast, easy and parallel detection of many types of interactions such as, antibody-antigen, protein-protein, protein-nucleic acid, protein-lipid, and protein-small molecule, and enzyme-substrate interactions, and according to Zhu showed great potential for drug discovery. Zhu provides a listing on page 59, Table 2, of known (note that Zhu was published in February 2003) detection methods used in protein microarray experiments. These methods are ELISA, isotopic labeling, sandwich immunoassay, SPR, non-contact AFM, planar waveguide, SELDI, and electrochemical. Applicant respectfully notes that no method that uses x-ray fluorescence to detect chemical binding in a protein microarray is described on the list. Thus, Applicant submits that the presently claimed invention provides a new and unobvious method for the detection of chemical binding. Applicant submits that at the time Zhu was published, which was almost two years after the present patent application was filed, there was still a long-felt need for a highly sensitive label-free

detection strategy for detecting chemical binding between binders and members of a receptor array (in this case, a protein array), and that no one had yet employed, or even suggested, a strategy of using x-ray fluorescence to detect chemical binding between binders and members of a receptor array (in this case, an array of proteins).

Predki was published about one year after Zhu. According to Predki, page 8 at the bottom of column 1 through the top of column 2, protein arrays are expected to aid in developing "...meaningful insights and discovery in biology..." in areas that include "...molecular interactions for protein functional characterization to optimization of drug-protein interactions, from profiling enzyme substrates to profiling enzymatic activities. Functional protein microarrays clearly have the potential to make significant contributions to both basic and applied research...". On page 10, at column 2, under the heading of DETECTION, according to Predki, "...most applications of functional proteome microarrays for interaction or substrate detection have employed some type of labeling strategy; usually fluorescent...colorimetric...or radioactive...". Furthermore, "...although label-free technologies, such as surface plasmon resonance...mass spectrometry...and others, are highly desirable, their availability and sensitivity have not been high enough to have come into common use for functional protein microarrays...". Finally, Predki states that "...regardless of the physics employed, the development of practical, robust and sensitive, label-free detection strategies will be tremendously valuable...". Predki does not describe any method that uses x-ray fluorescence to detect chemical binding between binders and members of a microarray (a protein array, for example). Applicant submits that at the time Predki was published, which was almost three years after the present patent application was filed, there was still a long-felt need for a highly sensitive label-free detection strategy for detecting chemical binding between binders and members of a receptor array (in this case, a protein array), and that no one had yet employed, or even suggested, a strategy of using x-ray fluorescence to detect chemical binding between binders and members of a receptor array (in this case, an array of proteins).

As still further evidence of non-obviousness and of the long-felt need in the art for the presently claimed invention, Applicant is submitting a letter from Dr. Gregory Cuny, who is the Director of Medicinal Chemistry in the Laboratory for Drug Discovery

in Neurodegeneration at Brigham & Women's Hospital, Harvard Medical School. The letter was written in support of a submission for an R&D 100 award to MESA (Measurement of Enzyme-Substrate Affinities), which is a trade name of an embodiment of the presently claimed method. According to Dr. Cuny, "...the measurement of protein-drug interactions is key to target-based drug development. These measurements are often difficult to obtain, especially when a mixture of proteins is used. "Label-free" fluorescence or fluorescence measurements obtained without the need for chemically appended fluorescing functional groups, is a significant improvement in the drug identification process. MESA technology (Measurement of Enzyme-Substrate Affinities) is an elegant solution to this unmet need for label-free drug measurement. It works by using x-ray excitation and x-ray fluorescence of heavy atoms. Many drugs contain these heavy atoms that are fluorescent in the x-ray spectrum. Label-free protein drug interaction measurements provide a means to answer questions concerning protein target identification during drug discovery and development. Utilizing phenotype cell-based assays is appealing from a drug discovery point of view. However, one drawback to this approach has been subsequent identification of the molecular target responsible for a particular compound's mechanism of action. Increasingly, regulatory agencies such as the FDA requires that the protein target be identified in order to grant Investigational New Drug (IND) states, i.e. approval for human clinical trials. Traditionally, this has involved chemical modification of the ligand with a fluorescent label. However, in many instances installation of the label results in diminished activity of the derivative compared to the parent molecule. MESA can allow label-free measurement of protein-drug interaction useful for target identification. This could unlock tremendous value by simplifying the process of target identification and would encourage increased utilization of cell-based assays in drug discovery. Label-free measurement of protein-drug interaction has been a longstanding need in the pharmaceutical industry. The preliminary MESA data is promising, and if it can be implemented on an industrial scale, it could significantly affect the development of new lifesaving drugs...". The R&D100 awards are given to a set of inventions that R&D Magazine deems the most important *new* products in a given year; an R&D 100 award was received for the technology of the presently claimed

invention in 2005. This is further evidence of the long-felt need of the label-free measurement technique described in the present patent application. Applicant is also submitting a paper that describes the R&D 100 award to MESA.

As further support of non-obviousness, Benjamin P. Warner, the first named inventor acquired several million dollars in start-up capital, successfully competed for a license to the invention, and after a successful career at Los Alamos National Laboratory, separated from the laboratory and formed a company (CALDERA PHARMACEUTICALS, INC., hereafter referred to as CALDERA) that is using the invention. Currently, the company is located at the following address:

Caldera Pharmaceuticals, Inc.
3491 Trinity Drive, Suite B
Los Alamos, NM 87544
Phone: 505-412-2345
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Dr. Warner is the CEO and president of CALDERA. CALDERA has also received several million dollars of additional in funding for the construction of a major biotech facility in Los Alamos for the company. Such financing is relatively rare, and is given to promote economic development in New Mexico. CALDERA has grown to more than 10 employees in the past several months and this number is expected to increase to approximately 100 personnel. The commercial success of CALDERA is directly tied to the claimed invention, and this commercial success also shows that the invention addresses a long-felt need in the pharmaceutical industry.

For all of the above reasons, Applicant submits that claims 1-20 are not obvious over Pirrung in view of Wang and Yokhin and Applicant urges that the rejection of claims 1-20 under 35 U.S.C. §103(a) over Pirrung in view of Yohkin should be withdrawn.

Applicant respectfully requests that this amendment be entered into the present patent application.

For the reasons set forth above, Applicant believe that all currently pending claims are in condition for allowance, and such action at an early date is earnestly solicited. No new matter has been added by the above changes. Reexamination and reconsideration are respectfully requested.

Respectfully submitted,

Date: January 16, 2007

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